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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,002	08/02/2001	Stephen Anderson	RU-0115	4899

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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,002	ANDERSON ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *03/04/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

The claims do not receive benefit of priority to the parent application 09/181,601 because the parent lacks descriptive support for the new element of "NOESY-assign process" of the current specification, as far as the examiner can determine. The examiner reviewed the parent application, and could not find basis for this limitation in the specification of 09/181,601.

Claim Rejections - 35 USC § 112

1. The rejection of claim 9 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by the University of Texas at Galveston campus as evidenced by Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480).

4. The examiner takes official notice that one year before the filing date of this application, the University of Texas at Galveston campus comprised a computer, an NMR facility which had a spectrometer, data collection device, and computer algorithms to analyze the NMR spectra and determine the tertiary structure of the proteins

including the NOAH program for automated assignment of NOESY spectra, as well as laboratories for expressing proteins, access to the Wisconsin programs which can parse target polynucleotides, and internet access to the Protein Data Bank and the DALI webserver.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480).

Wallace teaches a method for determining a biochemical function of a protein or polypeptide domain of unknown function (abstract) comprising: a) identifying a putative

polypeptide domain that properly folds into a stable polypeptide domain having a definite three dimensional structure, b) determining the three dimensional structure of the stable polypeptide domain (page 1004-5, subheading "derivation of 3D templates"), c) comparing the determined three dimensional structure to known three dimensional structures in the protein data bank, wherein said comparison identified known homologous three dimensional structures (page 1009, subheading "search for Ser-His-Asp triads in other PDB entries"), d) correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain (page 1009, figure 5 and page 1011, columns 1 and 2).

Wallace teaches identification of domains, but arguably does not teach the use of domains of 50 to 300 amino acids in length for comparison purposes. Further Wallace does not teach analysis of the structure by a NOESY-assign process in step (b).

Mumenthaler teaches an automated method of assignment of NOESY spectra and automatic calculation of the three dimensional structure by NMR (see abstract).

. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace with the NOESY assignment method of Mumenthaler since Mumenthaler states ""We regard our method as a highly practical tool for automatic calculation of three dimensional protein structures from NMR spectra with minimal human interference (abstract)". Thus, an ordinary practitioner would have been motivated to determine the 3D structures used by Wallace for analysis by the automated method of Mumenthaler since the method is a highly practical tool which

results "In practice, the work required to assign NOESY spectra is dramatically reduced by applying our automated method (page 466, column 2)".

8. Claims 1-5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479).

Wallace in view of Mumenthaler teach the limitations of claims 1, 5, 6 and 11 as discussed above. Wallace in view of Mumenthaler does not teach a prestep of parsing a database to identify the protein coding regions.

Farber teaches a method of discriminating open reading frames (abstract and pages 472-474).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace in view of Mumenthaler with the database preparation method of Farber since Farber notes "Simple neural networks predict coding regions in DNA very well when trained on a representation of DNA using single codon frequencies (page 478, column 1)". An ordinary practitioner would have been motivated to combine the method of Wallace in view of Mumenthaler with the protein coding determinations of Farber in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

9. Claims 1, 5, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480) and further in view of Friedrichs (J. Biomol. NMR (1994) 4:703-726)

Wallace in view of Mumenthaler teach the limitations of claims 1, 5 and 11 as discussed above. Wallace in view of Mumenthaler determines the three dimensional structure of the stable domain by reference to a protein database and suggests the use of NMR. However, Wallace in view of Holm does not teach the specific NMR characterization techniques nor automated NMR assignments.

Friedrichs teaches determination of the correctness of a protein structure using a variety of NMR spectrometer spectra (page 705) and automated analysis of these spectra using a computer program (pages 708-715). Friedrichs further teaches amide hydrogen exchanges (pages 705 and 708).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace in view of Mumenthaler with the use of NMR structural determination of Friedrichs since Wallace states "This suggests that the development of databases of 3D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions (abstract)". Here, Wallace expressly motivates the determination of new protein structures. Motivation to use NMR in this determination is provided by Mumenthaler as discussed above and by Friedrich,

who states "The choice of NMR experiments was based on considerations regarding the sensitivity and resolution of spectra for medium to large-sized proteins (page 720)". Friedrich further motivates the automated assignment of NMR spectra in this determination, noting "Instead of taking weeks, the backbone assignments can be made in one or two days following data acquisition and processing (page 722)". An ordinary practitioner would have been motivated to utilize NMR to determine protein structures in order to sensitively and accurately provide data for 3D determinations and would have been motivated to utilize the automated assignments of Friedrichs in order to minimize the time needed to determine the 3D structure as expressly motivated by Friedrichs.

10. Claims 1, 5, 7, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480) and further in view of Bagby et al (J. Biomol. NMR (1997) 10:279-282).

Wallace in view of Mumenthaler teach the limitations of claims 1, 5 and 11 as discussed above. Wallace in view of Mumenthaler do not teach the button test for microdialysis and NMR.

Bagby teaches a method for preparing samples for NMR to determine optimal solubilization comprising the steps: a) preparing an array of microdialysis buttons with 5 ul containing at least 1 mM protein (page 280), b) dialyzing each member of the array against a different buffer (page 280), c) analyzing the sample to determine if the protein

remained soluble (page 280) and d) selecting the optimum solubility for NMR (page 280). Bagby expressly notes a lab expressed the desired protein (page 281, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the button test of Bagby with the NMR and functional determination method of Wallace in view of Mumenthaler since Bagby states "The button test is an efficient, small scale way of tackling this problem.(page 281, column 1)". An ordinary practitioner would have been motivated to utilize the button test to optimize solubility for NMR since it is expressly noted as efficient and small scale, which reduced time and wasted reagents, which for purified proteins can represent a large investment of time and money.

11. Claims 1, 5 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480) and further in view of Holm et al (TIBS (1995) 20:478-480).

Wallace in view of Mumenthaler teach the limitations of claims 1, 5 and 11 as discussed above. Wallace in view of Mumenthaler do not teach the use of the DALI program or the protein data bank.

Holm teaches determination of three dimensional structures by cyrstallography or NMR (page 478, column 3) followed by database analysis using the complete three dimensional structure of the protein including every amino acid by DALI (page 478, column 3 and page 479). Holm exemplifies a comparison between urease and

adenosine deaminase (figure 1) in which the complete three dimensional structrures of the 352 amino acid adenosine deaminase protein is compred to the larger urease protein. Holm further shows a comparison which was performed for the Adenovirus type 5 knob domain (see page 478, table 1) which knob domain represents amino acids 386 to 581 of the Adenovirus fiber protein, resulting in a comparison of 195 amino acids, within the claim domain size range.

Further it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function detemination method of Wallace in view of Mumenthaler with the NMR technique taught by Holm and well known in the art for structure determination purposes and with the use of domains within the range of 50-300 amino acids since Holm teaches screening domains of those sizes. An ordinary practitioner would have been motivated to utilize database analysis of Holm in the method of Wallace since Wallace states "As the number of known protein structures increases, so the need for a 3D equivalent of PROSITE grows with it, especially for likely functions of proteins whose biological role is unknown (page 1001, column 1)". Thus, Wallace expressly notes that there is a need for methods of 3D comparison of proteins in order to determine the biochemical function of unknown proteins. Holm satisfies and answers this need to determine the relatioship of unknown to known proteins. Holm states "At the last stages of solving a new protein structure, crystallographers and nuclear magnetic resonance (NMR) spectroscopists are keen to know if their structure represents a unique protein fold or if it has an unexpected structural similiarity to a known protein fold. To answer these questions, the DALI

server performs a database search with a new structure against all structures in the Protein Data Bank. (Page 478, column 3)". Thus, Holm expressly notes that the ordinary practitioner in this art is motivated to perform a comparison to determine the relationship of the new protein with proteins present in the database, thereby fulfilling the stated need and motivation of Wallace.

12. Claims 1, 5, 8-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al (Protein Science (1996) 5:1001-1013) in view of Mumenthaler et al (J. Mol. Biol. (1995) 254:465-480) and further in view of Holm et al (TIBS (1995) 20:478-480) and further in view of Farber et al (J. Mol. Biol. (1992) 226:471-479).

Wallace in view of Mumenthaler and further in view of Holm teach the limitations of claims 1, 5 and 8-11 as discussed above. Wallace in view of Mumenthaler and further in view of Holm do not teach the use of parsing programs.

Farber teaches a method of discriminating open reading frames (abstract and pages 472-474).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace in view of Mumenthaler and further in view of Holm with the database preparation method of Farber since Farber notes "Simple neural networks predict coding regions in DNA very well when trained on a representation of DNA using single codon frequencies (page 478, column 1)". An ordinary practitioner would have been motivated to combine the method of Wallace in view of Mumenthaler and further in view of Holm with the protein coding

determinations of Farber in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

Response to Arguments

13. Applicant's arguments filed February 18, 2003 have been fully considered but they are not persuasive.

Applicant first argues that the priority should be granted. It appears that Applicant is mixing up two different priority issues. The case is a Continuation in Part, and this type of filing is, of course, permissible. However, the issue of priority of the claims, particularly as regards descriptive support, is not answered solely by the filing of a CIP. As MPEP 2133.01 notes "When applicant files a continuation-in-part whose claims are not supported by the parent application, the effective filing date is the filing date of the child CIP." Thus, for purposes of the prior art, since the parent application does not have descriptive support for the term "NOESY assign process", the effective filing date for these claims is the filing date of the current application.

Applicant argues that Mumenthaler does not teach a parsing step and that Mumenthaler studied known proteins. These arguments are not persuasive for several reasons. First, with regard to claim 12, this claim is not a method claim but is a product claim drawn to a system. Therefore, to the extent that the prior art teaches the structural limitations, the prior art meets the claim. Mumenthaler, and certainly the university, had access to B LAST and the Wisconsin programs, which both are programs "capable of" parsing polynucleotides. Since the claim is to the integrated system, the product, and not to the method, only the structural element is required.

Second, the word "unknown" is clearly an intended use recitation. It has no structural impact on the system whatsoever. As MPEP 2111.02 notes "Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." It is clear that a structural difference must exist between the claimed invention and the prior art to overcome the rejection and not simply a difference in the intended use. As MPEP 2111.02 also notes "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Here, no structural difference is imported by studying "unknown" as versus "known" proteins.

Applicant then argues that Wallace does not teach an essential step of the invention, identification of a protein domain.that folds into a defined three dimensional structure. This argument is not persuasive in view of Wallace's characterization of the Ser195-His57-Asp102 catalytic triad domain (page 1004, column 1), in which Wallace shows a three dimensional putative polypeptide domain which is composed of at least 195 amino acids (Ser195 being included).

Applicant then argues the word "unknown" and specifically, that Wallace does not teach addressing an "unknown" protein. This is expressly incorrect. Wallace expressly states "It is well established that sequence templates (e.g.. PROSITE) and databases

are powerful tools for identifying biological function and tertiary structure for an **unknown** protein sequence. Here we describe a method for automatically deriving 3D templates from the protein structures deposited in the Brookhaven Protein Data Bank. (emphasis added) (abstract)." Thus, Wallace expressly contemplates identifying domains of unknown proteins.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is cited in each of the rejections relying upon Mumenthaler and Farber. For example, an ordinary practitioner would have been motivated to determine the 3D structures used by Wallace for analysis by the automated method of Mumenthaler since the method is a highly practical tool which results "In practice, the work required to assign NOESY spectra is dramatically reduced by applying our automated method (page 466, column 2)". This represents a motivation to combine the references, since the ordinary practitioner would reduce work required to develop data for analysis by the Wallace method in order to identify unknown protein structures as expressly taught by Wallace.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers

for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

March 19, 2003